2. The paragraph at the top of page 12 is being deleted because it is unneeded and confusing in view of the text at page 11, lines 19-23. Claim 1 recites compounds in which the A ring is a substituted 6 membered aromatic ring (not a heteroaromatic ring) and the substituent T may be one of four groups. The subject matter of claim 1 is supported elsewhere in the specification, at pages 22 and 23.

3. Insertion of the word "or" between the last two members of the list of the defined D groups corrects a clerical error.

4. The amendment at page 12, line 21 corrects a textual discontinuity.

5. The amendment at page 13, line 1, inserting "preferably" is necessary in view of the broader definition of the E group given on page 12, line 11.

6. Support for the definition of R^{11} is to be found at page 38, lines 18-21. That text states that amides of the acids of the invention can be prepared from the acids by treatment with a primary or secondary amine, and the amine may be a simple alkyl amine. (The top of page 39 also states that the amine component may be an arylalkyl amine or an amino acid derivative in which the carboxyl group is blocked and the amine group is free. However, this language relating to arylalkyl amines and amino acid derivatives is not being used in the definition of R^{11} on page 13 at the present time because to do so might require re-defining the group R^{11} as used in a number of the partial structures shown at the bottom of page 19.

Support for the definition of R^{12} is to be found in synthetic method B and the associated explanatory text. General method B involves the malonic acid synthesis, in which lower alkyl esters of malonic acid are employed.

7. Support for the definition of R^{1} is to be found on page 15, line 3.

8. The text deleted from the bottom of page 14 is duplicated on page 15.

9. The text deleted at the top of page 15 appears to be a duplicate of the final partial structure from the set of structures on page 14, lines 8-11, as well as the definition of R^1 which was omitted from page 14. The structure at the top of page 15 is superfluous and the text on line 3 of page 15 has been inserted at the appropriate point on page 14.

The amendments to the text at page 15, lines 14-16 clarify that the text is intended to refer to the portion $(T)_xA$ of the general formula (L). The statement that T is a substituted acetylenic moiety has been deleted since this is a preferred substituent which is one of several identified as "most preferred" in the text near the bottom of page 22. The term "preferably" is appropriate in view of the statement on page 11 that x represents the number of substituent groups, and the text at the bottom of page 22 states and shows that the most preferred compounds of the generalized formula (L) have one substituent T.

The amendment on page 15 deleting the paragraph between lines 17 and 21 is to remove this paragraph from page 15. It will be reinserted at page 16 between lines 17 and 18 by a later amendment in due course.

The text fragment deleted from the bottom of page 15 is already repeated correctly at page 16 lines 18-19.

10. The text deleted from page 16, lines 1-12 does not appear to follow from page 16, and accordingly is being deleted as erroneous or superfluous. On page 16, line 13, the word "also" appears to be superfluous.

The amendment to the structure at line 14 of page 16 is to change the subscript "n" to " n' " to avoid a conflict between different definitions of the subscript "n".

The amendment to page 16, line 15, replacing "n" with " n' " is to avoid a conflict in the definition of the subscript "n".

The amendment to page 16, line 17, replacing "n" with " n' " is to avoid a conflict in the definition of the subscript "n".

The insertion of the paragraph between lines 17 and 18 of page 16 is the insertion

of the paragraph removed from page 15, lines 17-21.

11. The amendment at page 17, line 7, is to make clear that the text following relates to an alternative embodiment.

The structure at page 17, line 9 has been amended to change the subscript r to r', to prevent conflicting definitions of the subscript "r".

The subscript "r" has been changed to " r' " to prevent a conflict in the definition of "r".

12. The amendment to page 17, line 17 is to delete unnecessary and possibly incorrect text.

13. The amendment to page 18, lines 5-6 is to delete unnecessary and possibly incorrect text.

The structures at page 18, line 8 have been amended to change the subscript n to a subscript n" to prevent conflict in the definition "n".

The amendment to page 18, line 9 is to prevent a conflict in the definitions of "n".

The substitution of "a" by "the" in line 13 represents an improvement in English usage.

The revisions on page 18, line 13, clarify that the group "E" is that portion of the formula located between the D and G groups, but does not include either D or G.

The amendment to page 18, line 24, is to delete superfluous language.

14. The text on page 19, lines 1-18, is deleted as being a fragment of text which is now superfluous in view of other missing related textual material.

The amendment to the language of page 19, line 20 is to remove language more suited for use in a claim and replace it by common English.

The amendment in line 22 replacing the comma by a period is to correct punctuation.

15. The deletion of the second full paragraph of page 21 is to remove text which duplicates

text which is now located on page 16, between lines 17 and 18 of the specification. The insertion of the term "alternative" at page 21, line 13, is a clarifying revision.

The formula at page 21, line 16 has been revised to change the subscript "r" into " r' " to avoid conflicts in the definitions of "r". The change of "r" to " r' " in line 17 is to prevent conflict in the definitions of "r".

The amendment to page 21, line 20 in the structural formulae is to amend the definition of the subscript "n" to avoid conflicts in the definition of that term.

The revision of "n" to " n" " in line 21 is for consistency with the above structures and to prevent conflict in the definitions of "n".

16. The amendment to the structures MII-A, MI-A-3, and MI-A-4 on page 28 is to change the substituent group R^{14} to R^{40} for correspondence with the other formulae such as those on page 22, line 16, page 23, line 19, and claim 1.

17. The amendment to page 29, lines 2, 4, and 5 is to make the text consistent with the revisions to the equation at page 29, lines 7-9, discussed below.

Amendment of the chemical equation on page 29, lines 7-9 was to correct the first structure by inclusion of the necessary double bond of maleic anhydride and to change R^{14} to R^{40} in the other two structures, for consistency with terminology elsewhere in the application.

18. The revision at page 30, line 7, is to correct an obvious error. See the schematic for method B on page 31.

19. The correction to structural formula MI-F-I on page 36, line 10 is to delete the double bond in the ring. This double bond was present in the starting material MXXVI but is lost when the thiol reagent MXVII adds across it.

20. The revision to page 39, line 6 is to correct an obvious error in identifying the biphenyl

reagent starting material.

21. The revision to page 46, line I is to correct improper usage of the bracket symbol.

The amendment to page 46, line 2 removing the word "Author" corrects the failure to provide the name of the author at that point on the text.

Insertion of the parenthesis at page 46, line 2 completes the parenthetical expression begun on line I.

22. The structure at page 53, line 3, has been corrected to show the substituent group is R^{40} rather than R^{14}, for internal consistency.

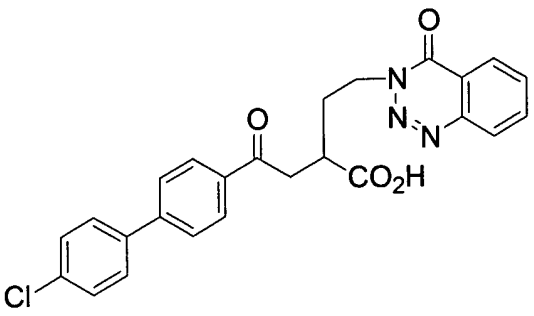
23. In the heading of the second column of the table, R^{14} has been replaced by R^{40} for internal consistency.

24. The structure at page 59, line 15 has been corrected to insert an inadvertently omitted nitrogen atom.

25. The heading of the table on page 67 has been corrected to avoid having two tables with the same heading. The units for the IC_{50} values have been inserted in the table's column headings.

Comments respecting the Official Action:

In the Official Action, the examiner imposed a restriction requirement and an election of species requirement. In response, the applicants elect restriction group I, drawn to compounds. Applicants further elect the species 4-(4'-chloro-biphenyl-4-yl)-4-oxo-2-[2-(4-oxo-4H-benzo[d][1,2,3]triazin-3-yl)ethyl]butyric acid, the structure of which is shown below:



In this application the applicants desire to claim the racemate and the separate enantiomers of the compound shown above, as well as pharmaceutical compositions containing them, and a method of using them to treat various conditions. It is respectfully suggested that the restriction requirement among group I (compounds), group II (compositions), and group III (methods) does not comport with the rules for restriction, and that it should accordingly be withdrawn.

The presently claimed compounds are generically covered by the claims of the parent case of this series, US patent 5,925,637, which issued 20 July 1999. Applicants now wish to claim the particular compounds, their pharmaceutical compositions, and their methods of use. If the examiner deems it necessary, a terminal disclaimer will be provided.

The racemate of the elected material was prepared in example 19 of the present application. The respective enantiomers of this material were separated and identified in the text as the compounds of examples 20 and 21. General method C of the application (page 32) provides information regarding the use of chiral HPCL to separate the enantiomers of racemic mixtures. Salts of the compounds of the invention are discussed in the specification at pages 39-40. The activity data for the compounds of examples 19, 20, and 21 are given in Table I, page 67 of the text.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

In view of the above amendments and explanations, this application is deemed to be in condition for allowance, and allowance is accordingly requested.

Respectfully submitted,

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Version with markings to show changes made:

In the claims:

Claim 1 has been cancelled and replaced by new claim 8.

Claims 2, 3, and 5 have been amended to refer to new claim 8 as shown below. Unamended claims 4, 6, and 7 are shown below for the convenience of the examiner.

2. (Amended) A composition having matrix metalloprotease inhibitory activity, comprising a compound of claim [1] 8 and a pharmaceutically acceptable carrier.

3. (Amended) A method of inhibiting matrix metalloprotease activity in a mammal comprising administration of an effective amount matrix metalloprotease inhibitor compound of claim [1] 8 to said mammal.

4. The method of claim 3 wherein said mammal is a human.

5. (Amended) A method of treating a mammal comprising administering to the mammal a matrix metalloprotease inhibiting amount of a compound according to claim [1] 8 sufficient to:

   (a) alleviate the effects of osteoarthritis, rheumatoid arthritis, septic arthritis, periodontal disease, corneal ulceration, proteinuria, aneurysmal aortic disease, dystrophobic epidermolysis, bullosa, conditions leading to inflammatory responses, osteopenias mediated by MMP activity, tempero mandibular joint disease, demyelating diseases of the nervous system;

   (b) retard tumor metastasis or degenerative cartilage loss following traumatic joint injury;

   (c) reduce coronary thrombosis from athrosclerotic plaque rupture; or

   (d) effect birth control.

6. The method of claim 5 wherein the effect is alleviation of osteoarthritis.

7. The method of claim 5 wherein the effect is retardation of tumor metastasis.

8. (New) A matrix metalloproteinase inhibitor selected from the group consisting of: (rac)-4-(4'-chloro-biphenyl-4-yl)-4-oxo-2-[2-(4-oxo-4H-benzo[d][1,2,3]triazin-3-yl)ethyl]butyric acid; (-)-4-(4'-chloro-biphenyl-4-yl)-4-oxo-2-[2-(4-oxo-4H-benzo[d][1,2,3]triazin-3-yl)ethyl]butyric acid; (+)-4-(4'-chloro-biphenyl-4-yl)-4-oxo-2-[2-(4-oxo-4H-benzo[d][1,2,3]triazin-3-yl)ethyl]butyric acid; and their pharmaceutically acceptable salts.

In the specification:

The accompanying marked-up copies of pages of the specification indicate the changes made therein.